REMARKS/ARGUMENTS

Status of the Claims

Claims 1-33 and 52-58 were rejected. Claims 34-51 have been withdrawn from consideration as being drawn to non-elected inventions and have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue these claims in a continuation or divisional application or to take other such appropriate action to seek protection of this canceled subject matter.

Claim 52 have been amended to clarify the invention. Support for this claim amendments can be found in the specification and claims as originally filed. No new matter has been added by way of these amendments.

Claims 1-33 and 52-58 are now pending in the present application. Reexamination and reconsideration of the claims are respectfully requested in view of the claim amendments and the following remarks. The Examiner's rejections in the Office Action are addressed below in the order set forth therein.

The Objections to the Specification Should Be Withdrawn

The Examiner has objected to the specification under MPEP 608.01 for containing embedded hyperlinks in various paragraphs of the application. Responsive to the Examiner's objection, the specification has been amended to remove all references to "http://" required to embed the hyperlink. Consequently, the URLs now contained in the specification are not hyperlinks or browser-executable codes, and the objection should be withdrawn.

The Examiner has further objected to the specification, particularly Figures 4-6 and parts of pages 24, 28, 29, 31, 33, 43, 51, 52, 56, 63-65, 67-69, 71, 72, and 80-82, for failing to identify the nucleotide sequences by appropriate sequence identifiers. Applicants, however, respectfully maintain that the sequences set forth on pages 24, 28, 29, 31, 33, 51, 52, and 56 are correctly presented in both the sequence listing and in the specification. The correct nucleotide sequences themselves have been provided in the sequence listing and appropriately identified with a sequence identifier in the specification. Applicants have at times included in the various nucleotide sequence listed in the application the sequence itself and any end modifications to the nucleotide sequence as utilized in the practice of the invention (e.g., "Bio"= 5' biotin label; "Pi" =

5' phosphate group; "NH_2"= 3' amino group, as outlined on page 28 of the originally filed application). The inclusion of these designations in the specification does not constitute a failure to comply with the sequence listing requirements of 37 CFR § 1.821 through 1.825 and MPEP 2422.02. Accordingly, in view of the above remarks, no amendments to the specification have been made to pages 24, 28, 29, 31, 33, 51, 52, and 56.

In regard to the Examiner's objection as to the nucleotide sequence provided on page 43 of the originally filed application (i.e., SEQ ID NO:10), Applicants have amended the specification to clearly indicate that the nucleotide designated "V" refers to a nucleotide selected from the group consisting of A, C, or G. As this information is already provided in the sequence listing, no amendment to SEQ ID NO:10 in the listing has been made.

A substitute Sequence Listing and a Notice to Comply with Sequence Listing Requirements under 37 CFR § 1.821 through 1.825 are submitted herewith in order to correct any omissions present on pages 63-65, 67-69, 71, 72, and 80-82 and in Figures 4-6. Furthermore, the specification has been amended to incorporate the appropriate sequence identifiers. Because the relevant sequences were presented in the figures and application as submitted on the filing date, no new matter has been added by way of these amendments or by submission of a Substitute Sequence Listing. Applicants respectfully submit that the objection to the specification and the Sequence Listing has been overcome and should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claim 52 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claim 52 has been amended to expedite prosecution. This rejection is respectfully traversed with respect to the amended claim.

The Examiner has indicated that is it unclear in claim 52 whether the newly synthesized first strand of cDNA is extended. For purposes of clarification, claim 52 has been amended to expressly recite "synthesizing the first strand of the nucleotide sequence by extending the 5' end region of the nucleotide sequence." Support for this claim amendment can be found at, for example, paragraph [0051] of the specification. In view of the claim amendment, Applicants

respectfully submit that the rejection under 35 U.S.C. § 112, second paragraph, has been obviated and should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 1-5, 8, 11, 26-28, 30, 32, 33, and 52-55 were rejected under 35 U.S.C. § 102(b) as being anticipated by Kinzler *et al.* (U.S. Patent No. 5,695,937; hereinafter "the '937 patent"). This rejection is respectfully traversed.

Independent claim 1, from which all of the other pending claim depend, is directed to a method for preparing a DNA fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA comprising preparing a nucleic acid that comprises a nucleotide sequence of the 5' end of an mRNA, attaching at least one linker to the nucleic acid, cleaving the nucleic acid with a restriction enzyme having its recognition site within the linker and its cleavage site within the nucleic acid corresponding to the 5' end of the mRNA, and collecting a resulting DNA fragment corresponding to the 5' end of the mRNA molecule. The Examiner maintains that the '937 patent teaches all of the steps recited in the claims. Applicants respectfully disagree with this conclusion.

The '937 patent discloses a method for Serial Analysis of Gene Expression (SAGE) that permits numerous transcripts to be analyzed in order to determine the overall gene expression pattern in various cell types. As a preliminary matter, the Examiner's attention is respectfully drawn to paragraphs [0005] through [0007] and [0010] of the present application which provide additional details regarding the differences between the SAGE method of Kinzler *et al.* and the current invention.

First, the '937 patent simply does *not* disclose a method that permits the identification and collection of DNA fragments corresponding to the 5' end of an mRNA molecule, as required by all of the pending claims. Specifically, the cited reference teaches that after cleaving the nucleic acid fragment bound to a bead with a tagging enzyme (TE), the resulting fragment has a primer, TE, and tag sequence. See, for example, Figure 1A of the '937 patent. The presence of the tag sequence necessarily indicates that DNA fragments corresponding to the actual 5' end of an mRNA molecule are not collected because the 5' or 3' end is still bound to a bead.

Moreover, careful analysis of the '937 patent further indicates that the cDNA sequences must be cleaved internally by utilizing a restriction enzyme. One of skill in the art would appreciate that the cleavage sites associated with such enzymes are *internal* sites within the nucleic acid molecule rather than at the ends of the nucleic acid and, therefore, do not permit the collection of DNA fragments corresponding to the actual 5' (or even the actual 3') end of an mRNA molecule. Thus, in light of this, the methods of the cited reference will typically identify sequences nearer the 3' end of the nucleic acid rather than that of the 5' end. Further evidence of this is provided in Velculescu *et al.* (1995) *Science* 270: 484-487. See, particularly, pages 484, right-hand column; page 486, left-hand column; and Table 2. A copy of this reference is submitted herewith in the Appendix for the Examiner's consideration. In contrast to the claimed methods, the cited reference simply does not teach a method for preparing and collecting a DNA fragment corresponding to the 5' end of an mRNA. Such methods are beneficial as they permit high-throughput gene expression analysis and profiling of transcriptional start points, neither of which may be accomplished by utilizing the SAGE method disclosed in the cited patent.

Applicants further note that the '937 patent teaches the use of a tag sequence that is fixed and defined for each RNA molecule. A fixed internal tag sequence, as described in the cited reference, necessarily prevents determination and capture of the 5' end of an mRNA molecule, as recited in the claims. The skilled artisan would understand the disclosure of the '937 patent to require internal cleavage of the DNA molecule to simplify the number of tag sequences. Again, this is simply not suitable for preparing and collecting a DNA fragment that corresponds to a nucleotide sequence of the actual 5' end region of an mRNA molecule.

Furthermore, in contrast to the methods of the cited reference, Applicants note that in, for instance, Example 1 and Figures 4 and 5 of the present application, cleavage of the nucleic acid fragment bound to beads with *MmeI* preserves the actual 5' end within the tag sequence. Accordingly, the present methods, unlike those disclosed in the '937 patent, permit the preparation and collection of DNA fragments corresponding to the 5' end of an mRNA.

According to the Federal Circuit, "anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration." *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Since the reference does not teach each and every element of the amended claims, particularly preparing and collecting DNA fragments

that correspond to the 5' end of an mRNA molecule, the '937 patent does not anticipate the methods of the invention. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. § 102(b) should be withdrawn.

The Examiner has further rejected claims 1, 2, 5-12, 14, 16-21, 23-32, 52-56, and 58 under 35 U.S.C. § 102(e) as being anticipated by Fischer *et al.* (U.S. Patent Application Publication No. 2004/0002104), which claims the benefit of U.S. Provisional Application No. 60/375,782 (filed April 26, 2002). This rejection is respectfully traversed.

Applicants respectfully maintain that the present rejection under 35 U.S.C. § 102(e) is improper. Specifically, 35 U.S.C. § 102(e) states that a reference is anticipatory if "the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States *before the invention by the applicant for patent*" (emphasis added). As noted above, the Fischer *et al.* reference claims priority to U.S. Provisional Application No. 60/375,782, which was filed on April 26, 2002. Applicants respectfully maintain, however, that this provisional application does not teach each and every element of claims 1, 2, 5-12, 14, 16-21, 23-32, 52-56, and 58. The reference should not be afforded the April 26, 2002 date for purposes of 35 U.S.C. § 102(e) for any disclosure that was not included in the provisional application but rather was added at the time the utility application was filed. Although Applicants do not concede that even the Fischer *et al.* application as filed on April 26, 2003 (published January 1, 2004) is anticipatory, the earliest date under 35 U.S.C. § 102(e) the patentees can rely on for any disclosure provided for the first time in the utility application is April 26, 2003.

In contrast, the instant application claims priority to Japanese Patent Application Nos. 2002-171851 (filed June 12, 2002) and 2002-235294 (filed August 12, 2002), thereby providing *prima facie* evidence that the claimed invention was invented by Applicants prior to the effective 35 U.S.C. § 102(e) date of the Fischer *et al.* reference (i.e., April 26, 2003, as discussed above). Therefore, the cited reference is not prior art under 102(e). Accordingly, the disclosure of the Fischer *et al.* patent application publication is not addressed substantively here, and the rejection under 35 U.S.C. § 102(e) should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 6, 9, and 31 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the '937 patent in further view of Maruyama *et al.* (1994) *Gene* 138:171-174. This rejection is respectfully traversed.

The '937 patent is described in detail above. The Maruyama *et al.* reference is directed to a method to replace the cap structure of an mRNA molecule with an oligoribonucleotide in order to label the 5' end of eukaryotic mRNAs. General methods for the isolation of *full-length* cDNA molecules are also provided. As noted above with the cited '937 patent, however, the Maruyama *et al.* reference does not teach or suggest the preparation and collection of a DNA *fragment* corresponding to the 5' end of an mRNA molecule of interest, as required by all of the current claims. Maruyama *et al.* may have appreciated the benefit of identifying the actual 5' end of an mRNA molecule, as noted in the article's introduction, but this statement is not equivalent to a teaching or suggestion of a method for accomplishing this objective.

A *prima facie* case of obviousness requires some suggestion to combine the cited references to arrive at the claimed invention and a reasonable expectation of success in such a combination. The Examiner broadly asserts that it would have been *prima facie* obvious to one of skill in the art to combine the method of the'937 patent with the oligo-capping procedures taught by Maruyama *et al.* to produce the methods of claims 6, 9, and 31 with a reasonable expectation of success because "the improved generation of 5' end-specific sequence tags would have improved the ability of the Kinzler *et al.* method to identify novel sequences in the 5' region of an mRNA sample" (see page 15, Office Action mailed October 4, 2006). Applicants respectfully disagree with the Examiner's conclusions and maintain that an insufficient motivation to combine the cited references has been provided. See *Ex parte Skinner*, 2 USPQ2d 1788, 1790 (B.P.A.I. 1986) (stating that "it is the duty of the examiner to explain why combination of the reference teachings is proper").

While Applicants maintain that the Examiner's reasoning is insufficient to establish a motivation to combine the references, even if combined, the cited references would not allow one of skill in the art to produce the claimed invention. As described above, neither reference teaches or suggests the required step of collecting a resulting DNA fragment corresponding to the 5' end of the mRNA. Contrary to the Examiner's assertions in the present Office Action, the

Maruyama *et al.* reference does not cure the deficiencies of the '937 patent identified above. Therefore, the disclosures of the cited references simply cannot be combined to produce the claimed methods, and claims 6, 9, and 31 are not obvious in view of Maruyama *et al.* and the '937 patent.

Claims 9, 10, 12, 14-16, and 58, all of which depend from claim 1, were further rejected under 35 U.S.C. § 103(a) as being unpatentable over the '937 patent in further view of Carnici *et al.* (1996) *Genomics* 37:327-336. This rejection is respectfully traversed.

The Carnici *et al.* reference is drawn a method for constructing high-content *full-length* cDNA libraries based on chemical introduction of a biotin group into the cap structure of a eukaryotic mRNA molecule. This reference does not teach or suggest a method for preparing DNA *fragments* corresponding to a nucleotide sequence of a 5' end region of an mRNA and in particular does not teach the required step of collecting a resulting DNA fragment corresponding to the 5' end of an mRNA molecule. Again, contrary to the Examiner's assertions, the Carnici *et al.* reference does not cure the deficiencies of the '937 patent, and the cited references could not be combined to arrive at the claimed methods. Therefore, claims 9, 10, 12, 14-16, and 58 are similarly not obvious in view of the Carnici *et al.* reference and the '937 patent.

Claims 13 and 57, both of which depend from claim 1, were also rejected under 35 U.S.C. § 103(a) as being unpatentable over the '937 patent in further view of Carnici *et al.* (1996) *Genomics* 37:327-336, Edery *et al.* (1995) *Mol. Cell. Biol.* 15(6):3363-3371, and Das *et al.* (2001) *Physiol. Genomics* 6:57-80. This rejection is respectfully traversed.

The teachings of the '937 patent and the Carnici *et al.* reference are described above. The Edery *et al.* reference discloses a method for isolating full-length cDNAs based on an mRNA cap retention procedure. The Das *et al.* reference is simply a review article that analyzes and compares a variety of techniques for isolating full-length cDNAs. As noted above with the other cited references, however, neither Edery *et al.* nor Das *et al.* teach or suggest the claimed methods of preparing a DNA fragment corresponding to the 5' end of an mRNA and, specifically, do not teach or suggest step (d) of independent claim 1 which requires collecting DNA fragments corresponding to the 5' end of the mRNA. In contrast to the Examiner's

conclusions, Applicants respectfully submit that the cited Edery *et al.* and/or Das *et al.* references do not cure the deficiencies of the '937 patent and the Carnici *et al.* reference. The disclosures of the cited references cannot be combined to produce the claimed methods. Accordingly, the combination of cited references could not have placed the invention of claims 13 and 57 in the hands of the public, and, therefore, the claims are not obvious.

Conclusion

Applicants respectfully submit that all the claims are in condition for allowance. Accordingly, a Notice of Allowance is respectfully requested in due course. If any minor informalities need to be addressed, the Examiner is directed to contact the undersigned attorney by telephone to facilitate prosecution of this case.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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